

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

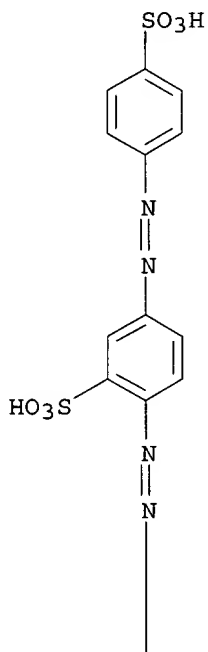
- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

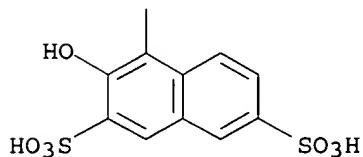
**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
 RN 6226-79-5 REGISTRY
 CN 2,7-Naphthalenedisulfonic acid, 3-hydroxy-4-[[2-sulfo-4-[(4-sulfophenyl)azo]phenyl]azo]-, tetrasodium salt (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN C.I. Acid Red 112, tetrasodium salt (8CI)
 CN **Ponceau S (6CI)**
 OTHER NAMES:
 CN C.I. Acid Red 112
 CN Ponceau Red S
 CN Ponceau S Extra
 MF C22 H16 N4 O13 S4 . 4 Na
 LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, CSCHEM, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, RTECS*, TOXCENTER, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 CRN (25317-44-6)

PAGE 1-A

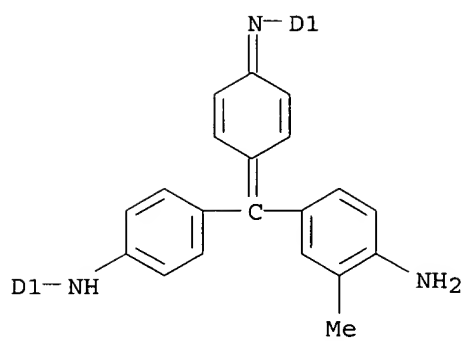


PAGE 2-A



4 Na

102 REFERENCES IN FILE CA (1962 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
102 REFERENCES IN FILE CAPLUS (1962 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

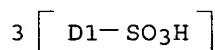
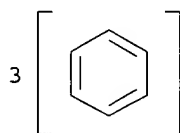


● 2 Na

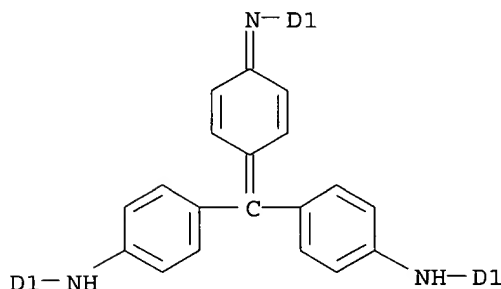
90 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 90 REFERENCES IN FILE CAPLUS (1962 TO DATE)

CN Water Blue IN
 DR 1324-79-4
 MF C37 H29 N3 O9 S3 . 2 Na
 CI IDS
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, CA,
 CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB,
 EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, MSDS-OHS, PROMT, RTECS*,
 TOXCENTER, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 CRN (30424-60-3)

PAGE 1-A



PAGE 2-A



● 2 Na

165 REFERENCES IN FILE CA (1962 TO DATE)
 4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 165 REFERENCES IN FILE CAPLUS (1962 TO DATE)
 15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L2 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2002 ACS
 RN 28631-66-5 REGISTRY
 CN Benzenesulfonic acid, aminomethyl[[4-[(sulfophenyl)amino]phenyl][4-
 [(sulfophenyl)imino]-2,5-cyclohexadien-1-ylidene]methyl]-, disodium salt
 (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN C.I. Acid Blue 22 (6CI, 7CI, 8CI)
 OTHER NAMES:
 CN Acid Blue 2BN
 CN Acid Blue 2R

CN Acid Blue 3B
CN Acid Blue 3R
CN Acid Blue R
CN Acid Blue S 2B
CN Acid Blue S 3R
CN Acid Blue SB
CN Acid Blue SGR
CN Acid Blue SR
CN **Aniline blue**
CN Aniline blue water soluble
CN C.I. 42755
CN Calcocid Blue 2R
CN Calcocid Blue 3B
CN Calcocid Blue B
CN Calcocid Blue R
CN Calcocid Ink Blue G
CN Calcocid Ink Blue R
CN China Blue
CN Cotton blue
CN Ink Blue A
CN Ink Blue CR
CN Ink

FILE 'REGISTRY' ENTERED AT 15:47:56 ON 20 JUN 2003

L1 0 S HEPARAN SULFATE/CN
L2 145 S HEPARAN SULFATE
L3 1 S HEPARAN/CN
L4 0 S L3 AND L2

FILE 'CAPLUS' ENTERED AT 15:50:32 ON 20 JUN 2003

L5 124 S L3
L6 27 S L3/USES
L7 2 S DEMETIA
L8 8108 S DEMENTIA
L9 5808 S (CORONARY HEART DIS?)
L10 35427 S ATHEROSCLEROSIS
L11 983 S HEAD INJURY
L12 0 S ISCHEMIC (3A) STROCK
L13 1645 S ISCHEMIC (3A) STROKE
L14 1141 S HEAD (3A) INJURY
L15 931 S ?CEREBR? HEMORRH?
L16 730 S HYDROCEPHALUS?
L17 2121 S PERIPHERAL NEUROP?
L18 52433 S L8 OR L9 OR L10 OR L14 OR L14 OR L15 OR L16 OR L17
L19 1 S L18 AND L5
L20 7438 S HEPARAN (2A) SULFATE
L21 224 S L20 AND L18
L22 129 S L20 (3S) L18
L23 105 S L20 (1S) L18
L24 22 S L23 AND TREAT?

=> save all

ENTER NAME OR (END):l09892308/l

L# LIST L1-L24 HAS BEEN SAVED AS 'L09892308/L'

=> save l24

ENTER NAME OR (END):a09892308/a

ANSWER SET L24 HAS BEEN SAVED AS 'A09892308/A'

=>

L26 ANSWER 13 OF 13 USPATFULL

SUMM U.S. Pat. No. 4,956,347, issued Sep. 11, 1990 to Ban et al. relates to the use of a mixture of "sulfomucopolysaccharides" comprising heparin, **heparan sulfate**-like substance, dermatan sulfate, and chondroitin sulfate A and C, for the **treatment** of patients suffering from Alzheimer's-type senile **dementia**.

PI US 5164295 19921117

DETD Likewise, chimeric HB-EGF antagonists can be generated which include at least the **heparan sulfate** chains of a syndecan. HB-EGF itself is a potent mitogen of smooth muscle cells. A chimeric protein comprising an antagonistic variant of HB-EGF and **heparan sulfate** glycosaminoglycan chains can be used in the **treatment** of such vascular diseases as **atherosclerosis**

PI US 5486599 19960123

L26 ANSWER 11 OF 13 USPATFULL

SUMM Proliferation of smooth muscle cells in blood vessel walls occurs in response to vascular injury, and in association with certain disease states (Austin, G. E., et al., J Am Coll Cardiol (1985) 6:369-375). The proliferation of these cells can have negative effects due to the production of excess proteins or other matrix molecules, which, along with the cells themselves, form pathologic lesions of, for example, **atherosclerosis**, renal hypertension, pulmonary hypertension, vasculitis, and post-surgical vascular restenosis. Thus, heparin/**heparan sulfate** has applications in the **treatment** of these diseases.

PI US 5795875 19980818

L26 ANSWER 1 OF 13 USPATFULL

SUMM [0017] Mucopolysaccharidoses are a group of inherited metabolic disorders caused by a deficiency in the lysosomal enzymes needed to break down mucopolysaccharides, long chains of sugar molecules used to build connective tissue and organs in the body. A deficiency in one or more of these enzymes causes a build up of excess amount in the body, causing progressive damage and eventual death. Among these disorders are Hurler, Scheie and Hurler/Scheie syndromes (the most severe form, occurs in infancy with death resulting before age 10 years, symptoms include clouding of the cornea and progressive physical and mental disability, caused by a deficiency in .alpha.-L-iduronidase), Hunter syndrome (affects juveniles with death usually resulting by age 15 years, symptoms include joint stiffness, mental deterioration, dwarfing and progressive deafness, caused by a deficiency in iduronate-2-sulfatase), Sanfillipo syndrome (death usually occurs by late teens, symptoms include progressive **dementia** and mental deterioration in childhood, caused by a deficiency in heparan N-sulfatase, .alpha.-N-acetylglucosaminidase, acetyl-CoA-glucosaminide acetyltransferase and/or N-acetylglucosamine-6-sulfatase), Morquio syndrome (appears in infancy, symptoms include severe dwarfing and corneal clouding, cardiac or respiratory disease may cause death in third or fourth decade of life, caused by a deficiency in galactosamine-6-sulfatase and/or .beta.-galactosidase), Maroteaux-Lamy syndrome (resembles Hurler syndrome, onset in infancy, but no mental disability, death usually occurs in second or third decade of life, caused by a deficiency in arylsulfatase B), and Sly disease (symptoms include corneal clouding, skeletal irregularities, and enlargement of the liver and spleen, caused by a deficiency in .beta.-glucuronidase). Hunter syndrome is particularly linked to a deficiency in iduronate-2-sulfatase, which catalyzes the breakdown of **heparan sulfate** and dermatan sulfate, and it has been suggested that this condition can be **treated** by administration of variant forms of the enzyme (U.S. Pat. No. 6,153,188). The digestive of particular interest, for example in therapy in humans and animals, therefore also include iduronate-2-sulfatase and functional mutants, variants and derivatives thereof.

PI US 2003049245

A1 20030313

L26 ANSWER 2 OF 13 USPATFULL

DETD In other instances, it may be desirable to administer syndecan antagonists, such as a mutant form of syndecan or a syndecan homolog which blocks at least one of the normal actions of syndecan. For example, **treatment** with certain syndecan antagonists can down-regulate the mitogenic activity of a heparin-binding growth factor (HBGF). Antagonists include syndecan homologs having altered **heparan sulfate** chains, such as those identified by combinatorial analysis (see section IV), as well as fusion proteins which inhibit the mitogenic activity of an HBGF by competitively binding its receptor, alternatively, by binding the HBGF itself and sequestering it. For instance, in the presence of the chimeric FGF-receptor/syndecan protein described below, the bFGF has reduced ability to mediate biological responses normally associated with it as it becomes sequestered by the chimeric FGF-receptor. Also, as described below, chimeric VEGF antagonists can be used to inhibit neovascularization of tumors, and chimeric HB-EGF antagonists can be used to inhibit smooth muscle proliferation in the **treatment** of **atherosclerosis**. Similar to the use of antagonistic syndecan antagonists, anti-syndecan antibodies can be used to decrease mitogenic levels of growth factors by preventing **heparan sulfate** binding.

DETD Likewise, chimeric HB-EGF antagonists can be generated which include at least the **heparan sulfate** chains of a syndecan.

HB-EGF itself is a potent mitogen of smooth muscle cells. A chimeric protein comprising an antagonistic variant of HB-EGF and **heparan sulfate** glycosaminoglycan chains can be used in the **treatment** of such vascular diseases as **atherosclerosis**

PI US 6531295 B1 20030311

L26 ANSWER 3 OF 13 USPATFULL

SUMM [0002] The present invention relates to methods and compositions for **treatment** of vascular conditions, particularly diabetes and **atherosclerosis**. The present invention is directed to methods and compositions for determining the expression or activity of enzymes affecting **heparan sulfate** proteoglycan and the use of therapeutic compounds that effect the expression or activity of these enzymes, particularly heparanase.

DETD [0080] **Heparan sulfate** plays a key role in kidney function, and heparanase expression is induced by diabetes-inducing and atherogenic molecules as shown in the Examples presented herein. Induction of heparanase expression was tested in tissues of mice which are used as a model for kidney disease. Mice which are deficient in leptin receptor (db/db mice), show a phenotype that is very similar to patients with type 2 diabetes mellitus. These mice are a useful model in which to study the pathogenesis and **treatment** of diabetic nephropathy. Mice deficient in apolipoprotein E (apoE) develop **atherosclerosis** and also develop kidney dysfunction. Heparanase expression in these two mouse models was compared with that of wild type mice.

PI US 2003036103 A1 20030220

L26 ANSWER 4 OF 13 USPATFULL

DETD [0016] The present invention comprises methods and compositions for detecting compounds or molecules that have specific biological effects and that may be useful as therapeutic agents. The present invention also comprises methods and compositions for the **treatment** and prevention of vascular occlusive conditions such as, but not limited to neointimal hyperplasia, restenosis, transplant vasculopathy, cardiac allograft vasculopathy, **atherosclerosis**, and arteriosclerosis. Such methods and compositions comprise methods for inhibition of smooth muscle cell (SMC) growth and proliferation, and for induction of quiescence in smooth muscle cells. Preferred embodiments of the present invention comprise methods and compositions for inducing **heparan sulfate** proteoglycan (HSPG) synthesis and expression, including, but not limited to, the induction of HSPGs such as syndecan, glypican and perlecan, and most preferably perlecan synthesis and gene expression.

PI US 2002182587 A1 20021205

L26 ANSWER 5 OF 13 USPATFULL

SUMM In view of the observation that heparanase activity is present in mobile, invasive cells associated with pathologic states, it may be hypothesized that an inhibitor of heparanase would broadly influence the invasive potential of these diverse cells. Further, inhibition of **heparan sulfate** degradation would inhibit the release of bound growth factors and other biologic response modifiers that would, if released, fuel the growth of adjacent tissues and provide a supportive environment for cell growth (Rapraeger et al., Science 252: 1705-1708, 11991). Inhibitors of heparanase activity would also be of value in the **treatment** of arthritis, asthma, and other inflammatory diseases, vascular restenosis, **atherosclerosis**, tumor growth and progression, and fibro-proliferative disorders.

DETD Inhibition of **heparan sulfate** degradation will also inhibit the release of bound growth factors and other biologic response

modifiers that would, if released, fuel the growth of adjacent tissues, and provide a supportive environment for cell growth (Rapraeger, et al., Science 252: 1705-1708, 1991). Inhibitors of heparanase activity would be of value in the **treatment** of arthritis, asthma, and other inflammatory diseases, vascular restenosis, **atherosclerosis**, tumor growth and progression, and fibro-proliferative disorders.

PI US 6387643 B1 20020514

L26 ANSWER 6 OF 13 USPATFULL

SUMM [0023] U.S. Pat. No. 4,956,347, Ban et al., issued Sep. 11, 1990, relates to the use of ATEROID, a mixture of "sulfomucopolysaccharides" comprising heparin, **heparan sulfate**-like substance, dermatan sulfate, and chondroitin sulfate A and C, for the **treatment** of patients suffering from Alzheimer's-type senile **dementia**. ATEROID is defined in the U.S. Pat. No. 3,000,787, Bianchini, issued Sep. 19, 1961, as a heparinoid anti-cholesterolemic factor. ATEROID, which is in some aspects similar to heparin, has essentially no anti-coagulant effect. The patent discloses that ATEROID can be extracted from the small intestine and particularly from the duodenum of mammals, by means of methods suitable for the isolation of aminopolysaccharidic or glycoproteic compounds.

PI US 2002004493 A1 20020110

L26 ANSWER 7 OF 13 USPATFULL

SUMM U.S. Pat. No. 4,956,347, Ban et al., issued Sep. 11, 1990, relates to the use of ATEROID, a mixture of "sulfomucopolysaccharides" comprising heparin, **heparan sulfate**-like substance, dermatan sulfate, and chondroitin sulfate A and C, for the **treatment** of patients suffering from Alzheimer's-type senile **dementia**. ATEROID is defined in the U.S. Pat. No. 3,000,787, Bianchini, issued Sep. 19, 1961, as a heparinoid anti-cholesterolemic factor. ATEROID, which is in some aspects similar to heparin, has essentially no anti-coagulant effect. The patent discloses that ATEROID can be extracted from the small intestine and particularly from the duodenum of mammals, by means of methods suitable for the isolation of aminopolysaccharidic or glycoproteic compounds.

PI US 6277874 B1 20010821

L26 ANSWER 8 OF 13 USPATFULL

SUMM U.S. Pat. No. 4,956,347, Ban et al., issued Sep. 11, 1990, relates to the use of ATEROID, a mixture of "sulfomucopolysaccharides" comprising heparin, heparan sulfate-like substance, dermatan sulfate, and chondroitin sulfate A and C, for the **treatment** of patients suffering from Alzheimer's-type senile dementia. ATEROID is defined in the U.S. Pat. No. 3,000,787, Bianchini, issued Sep. 19, 1961, as a heparinoid anti-cholesterolemic factor. ATEROID, which is in some aspects similar to heparin, has essentially no anti-coagulant effect. The patent discloses that ATEROID can be extracted from the small intestine and particularly from the duodenum of mammals, by means of methods suitable for the isolation of aminopolysaccharidic or glycoproteic compounds.

PI US 6245751 B1 20010612
WO 9801101 19980115

L26 ANSWER 9 OF 13 USPATFULL

DETD Pigeon smooth muscle cells provide an advantageous system in which to study **heparan sulfate** regulation of gene expression. This is due to the availability of SMC lines of White Carneau (WC) **atherosclerosis**-susceptible pigeons exhibiting enhanced growth compared with the SMCs of Show Racer (SR) pigeons as demonstrated by Bortoff and Wagner (1995, Mol. Biol. Cell. 6:13. Without wishing to be

bound by theory, gp180 may participate in a mechanism linked to enhanced cell growth and, perhaps, to susceptibility to **atherosclerosis**. The data disclosed herein demonstrate that SMCs **treated** with HS exhibit reduced gp180 gene expression. Although there may be other mechanisms for downregulating gp180 gene expression as demonstrated by the reduced gp180 expression in serum-starved growth-inhibited SMCs, the data disclosed herein demonstrating the specific downregulation of gp180 expression by HS suggest specific therapeutic approaches using heparin-like molecules.

PI US 6221855 B1 20010424

L26 ANSWER 10 OF 13 USPATFULL

DETD It was also demonstrated that the PS oligo S-dC28 inhibits human aortic SMC adhesion in vitro owing to a non-G-quartet, non-sequence specific mechanism. This inhibition can be partially reversed by fibronectin and completely reversed by laminin. In addition, the presence of serum in the culture media also diminishes the S-dC28-mediated inhibition of SMC adhesion. Taken together, these results suggest that PS oligos bind directly in a non-sequence specific manner to several critical proteins in the ECM such as laminin, fibronectin, **heparan sulfate** proteoglycans and bFGF, thereby inhibiting SMC adhesion. This property of the PS oligos may have ramifications for the **treatment** of disease processes involving SMC adhesion and motility including **atherosclerosis** and angioplasty restenosis.

PI US 5854223 19981229

L19 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

AN 1987:113552 CAPLUS

DN 106:113552

TI Therapeutic poly- and oligosaccharides, especially glycosaminoglycans

IN Robert, Ladislav; Hornbeck, William; Petitou, Maurice; Choay, Jean

PA SANOFI, Fr.

SO Eur. Pat. Appl., 35 pp.

CODEN: EPXXDW

DT Patent

LA French

IC ICM A61K031-725

CC 1-12 (Pharmacology)

FAN. CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 208623	A2	19870114	EP 1986-401562	19860711
	EP 208623	A3	19891227		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	FR 2584606	A1	19870116	FR 1985-10788	19850712
	JP 62018401	A2	19870127	JP 1986-163490	19860711
PRAI	FR 1985-10788		19850712		

AB Glycosaminoglycans (GAG) or GAG fragments are selective elastase inhibitors, esp. of leukocytic elastase and cathepsin G and increase the serum level of elastase. GAG can therefore be used for the treatment of certain connective tissue disorders. Heparin and the heparin fragments CY 222 and CY 216 inhibited collagen formation in vitro by smooth-muscle cells of the swine aorta.

ST connective tissue drug glycosaminoglycan; elastase inhibitor glycosaminoglycan

IT Mucopolysaccharides, biological studies

Oligosaccharides

RL: BIOL (Biological study)

(connective tissue disease treatment with)

IT Polysaccharides, biological studies

RL: BIOL (Biological study)

(connective tissue disease treatment with CY 216 and CY 222)

IT Blood serum

(elastase of, glycosaminoglycan effect on)

IT Collagens, biological studies

Fibronectins

RL: FORM (Formation, nonpreparative)

(formation of, inhibition of, by glycosaminoglycans)

IT **Atherosclerosis**

(treatment of, with glycosaminoglycans)

IT Blood vessel, disease or disorder

(treatment of, with glycosaminoglycans)

IT Brain, disease or disorder

(vascular, treatment of, with glycosaminoglycans)

IT Connective tissue

Joint, anatomical

(disease, treatment of, with glycosaminoglycans)

IT Lung, disease or disorder

(fibrosis, treatment of, with glycosaminoglycans)

IT Mucopolysaccharides, biological studies

RL: BIOL (Biological study)

(glycosaminoglycans, connective tissue disease treatment with)

IT 9004-61-9, Hyaluronic acid 9007-27-6 9007-28-7 24967-94-0

RL: BIOL (Biological study)

(connective tissue disease treatment by)

IT ~~9050-30-0, Heparan sulfate~~ 70226-44-7, Heparan

RL: BIOL (Biological study)

(connective tissue disease treatment with)

IT 9004-06-2, Elastase

RL: BIOL (Biological study)
(inhibition of, by glycosaminoglycanes, treatment of connective tissue
diseases in relation to)

IT 56645-49-9

RL: BIOL (Biological study)
(inhibition of, by glycosaminoglycanes, treatment of connective tissues
diseases in relation to)

=>